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Human Medicines Development and Evaluation

Assessment report

Rasilez, Sprimeo, Riprazo (aliskiren)
Rasilez HCT (aliskiren/hydrochlorotiazide)

Procedure No: EMEA/H/C/xxxx/WS/0069

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Aliskiren is an anti-hypertensive agent, which acts by inhibiting the enzyme renin to block the conversion of angiotensinogen to angiotensin I, the precursor of angiotensin II. Aliskiren at once daily doses of 150 and 300 mg was approved in the EU on 22 August 2007, for use as monotherapy, or in combination with other anti-hypertensive agents, for the treatment of mild to moderate hypertension.

On 16 January 2009, the new fixed combination aliskiren/hydrochlorothiazide (Rasilez HCT), was approved in the EU for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone, and as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

This application concerns the following medicinal products:

Medicinal product:	International non-proprietary name:	Presentations:
Rasilez	aliskiren	See Annex A
Sprimeo	aliskiren	See Annex A
Riprazo	aliskiren	See Annex A
Rasilez HCT	Aliskiren/HCTZ	See Annex A

The variation requested is the following:

Variations requested		Type
C.I.3.a	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	IB

In June 2010, the PhVWP released a report on the risk of angioedema with aliskiren containing a cumulative review of the risk in post-marketing experience with aliskiren. In their conclusions, the PhVWP recommended to update the aliskiren product information to reflect more accurately the risk of angioedema with aliskiren (see discussion below).

This type IB variation concerns an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration.

This application was submitted for a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

1.2. Clinical aspects

Angioedema

Background

Angioedema is an adverse reaction of the skin and subcutaneous tissue that can begin with signs suggesting a hypersensitivity reaction (in particular, difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue), and can develop rapidly and in rare cases can be dangerous if it affects the throat, since it can lead to obstruction of the airway.

Angioedema has been reported during the clinical trials with aliskiren and also in post marketing experience. Therefore it is mentioned as an identified risk in the RMP of Rasilez and Rasilez HCT, and consequently angioedema reports are closely monitored and analyzed in the respective PSURs as a RMP commitment.

In the SPC of Rasilez, Riprazo, Sprimeo and Rasilez HCT, angioedema is mentioned as a rare ADR under section 4.8. There is a contraindication in section 4.3 for patients with a history of angioedema under aliskiren and a special warning in section 4.4 for angioedema under aliskiren.

During the March 2010 PhVWP meeting a concern was raised by Afssaps regarding one case of angioedema that occurred in France in a patient taking aliskiren who had a medical history of angioedema under the ACE inhibitor perindopril. The patient had an aminopeptidase P activity deficiency (58%) which increases the risk of kinine accumulation.

Aliskiren is not expected to inhibit ACE-dependent degradation of vasoactive peptides (bradykinin, substance P). The mechanism underlying development of angioedema is unknown.

Following a preliminary discussion at the PhVWP, a cumulative analysis has been performed on the data provided in the Rasilez, Riprazo, Sprimeo and Rasilez HCT PSURs in order to evaluate the need to add any information in the SPCs on the risk of angioedema in patients with a history of angioedema.

Cumulative analysis of Angioedema

This cumulative review focused on the reported rate of angioedema or angioedema-type reactions (reported as localized periorbital, lips, tongue, face or throat oedema with/without urticaria or pruritus) and spontaneous cases of potentially greater severity/specificity described in PSURs 1-5 of Rasilez, Riprazo, Sprimeo and PSURs 1-2 of Rasilez HCT, with particular regard to cases with a medical history of angioedema/angioedema-like reactions.

Cumulative results from PSURs 1- 5 of Rasilez (5 May 2007-30 Sept 2009)

In the PSURs 1-5 of Rasilez, there were cumulatively 300 reports (including 234 spontaneous cases from HCP) of angioedema/anaphylaxis reports, in over 530,000 PTYs, that translated into a reporting frequency of 0.57 per 1000 PTYs. The reporting frequencies of angioedema/anaphylaxis reports in the last two PSURs decreased to 0.33 per 1000 PTYs compared to the overall reporting frequency of 0.57 per 1000 PTYs (PSUR 1-5). Cumulatively there were:

226 serious cases, out of which there were:

- 114 cases with a final diagnosis of angioedema;
- 112 cases with symptoms clinically similar to angioedema without a final diagnosis;
- 104 cases with positive dechallenge (DC+);
- 1 case with fatal outcome;
- 56 reports of angioedema/angioedema-like reactions with a history of angioedema/angioedema like reactions, out of which about 30 cases with a medical history of angioedema/angioedema-like

reactions on ACE inhibitors or ARB, 1 cases with potential hereditary angioedema due to C1 esterase inhibitor low level;

41 cases with RAS blockers co-administered (2 cases ACE inhibitors; 9 cases ARBs; 1 case both).

Literature

An overall incidence rate (IR) of 1.97 angioedema cases per 1,000 PTY in patients newly prescribed with ACE inhibitors has been reported. In a comparison group of initiators of other oral antihypertensive drugs, an angioedema IR of 0.51 per 1,000 PTY is reported. In addition, the angioedema IR is reported as 0.99 per 1,000 PTY in users of ARBs (Miller et al, 2008).

The cumulative reporting rate for aliskiren in the PSURs appears to be lower (0.57 per 1000 PTY) than the IR for ACE inhibitors and ARBs known from the literature, 1.97 and 0.99 per 1000 PTY, respectively.

Cumulative results from PSURs 1-2 of Rasilez HCT (18 Jan 2008 - 18 Jan 2010**)**

Cumulatively, a total of 70,800 PTY were reported.

A total of 14 cases of symptoms that were clinically similar to angioedema were reported.

In 2 cases a history of hypersensitivity type reaction or angioedema like reaction was reported.

In 1 case there was a co-administration of ARB.

In 3 cases there was positive dechallenge (DC+).

Taking into account the cumulative patient exposure of approximately 70,800 patient years, the reporting rate is approximately 0.13 per 1000 PTY, which is below the mentioned rates in literature for ACE inhibitors (1.97 per 1,000 PTY) or for ARB (0.99 per 1,000 PTY) (see the reference above).

Discussion

Cumulatively, in post marketing experience a total of 300 cases of angioedema/angioedema like reactions and a total of 14 cases of symptoms that were clinically similar to angioedema have been reported respectively in PSURs 1-5 of Rasilez and PSURs 1-2 of Rasilez HCT.

In particular, 56 reports of angioedema/angioedema-like reactions that had a history of angioedema/angioedema like reactions were described in PSURs 1-5 of Rasilez, out of which about 30 cases had a medical history of angioedema/angioedema-like reactions on ACE inhibitors or ARB.

There were over two dozen cases of angioedema with a medical history or diagnosis of angioedema, including those reported in this PSUR 5 period.

In addition, out of 14 cases with symptoms that were clinically similar to angioedema reported in PSURs 1-2 of Rasilez HCT, in two cases a history of hypersensitivity type reaction or angioedema like reaction was reported (one on ARB).

Moreover, cumulatively a total of 41 cases reported a co-administered ACE inhibitor or ARB in PSURs of Rasilez and one additional case was reported in PSURs of Rasilez HCT in which aliskiren was administered with a ARB.

Although angioedema is an adverse reaction of the skin and subcutaneous tissue that is already described in the the MAH's CSD and SPCs of Rasilez, Riprazo, Sprimeo and Rasilez HCT in the relevant sections (4.3, 4.4 and 4.8), no information is provided on the risk of angioedema/angioedema like reactions in patients that have experienced angioedema or symptoms like angioedema in the past.

Conclusions

In post marketing experience of aliskiren (PSURs 1-5 of Rasilez and PSURs 1-2 of Rasilez HCT) there are cases of angioedema in patients with a history of angioedema whatever the aetiology including a previous exposition to ACE inhibitors and ARBs.

Case reports, case series, post marketing adverse reaction data and literature data demonstrate that there is some degree of angioedema-cross reactivity between the classes of RAS blocking agents. Therefore, the potential for aliskiren-induced angioedema in patients with a history of angioedema under ACE inhibitors or ARBs cannot be excluded.

Given the potential life-threatening nature of angioedema, even if the exact mechanism of angioedema induced by these medications has not been fully elucidated, these data suggest that caution should be used when initiating aliskiren therapy in patients who previously developed angioedema with ACE inhibitors or ARBs therapy.

Considering the prevalence, albeit low, of angioedema cross–reactivity described in the literature (<10%) between ACE inhibitors and ARBs (Arch Intern Med. 2004; 164:910-913; Lancet 2003; 362:772-776), and the potential for aliskiren-induced angioedema in patients with a history of angioedema under ACE inhibitors or ARBs, close monitoring is necessary to ensure that angioedema does not occur again under aliskiren. Moreover, patients with a history of angioedema in general (idiopatic or hereditary or under other medicines) may be at increased risk of angioedema while receiving a RAS blocking agent, including aliskiren. Therefore, caution and close monitoring should be recommended when aliskiren is prescribed in these cases.

The additional comments below were raised during the discussion:

- There was uncertainty regarding the incidence of angioedema reported by the MAHs in the PSURs for Rasilez and therefore further data are considered necessary. Although it was acknowledged that it would be difficult to design an appropriate study given the rarity of the ADR angioedema, the PhVWP/CHMP was of the view that the MAH for Rasilez and Rasilez HCT should be asked to make a proposal for such a study in the context of the next RMP update to explore the risk further.
- The PhVWP/CHMP was informed of an independent cohort study that is currently being conducted in Germany, with relatively correct exposure data, and which would generate further data on risks with aliskirens e.g. angioedema within approximately 2 years.
- The working party/CHMP was of the view that the MAH should be asked to elaborate further on the underlying biological mechanism of action for these reactions and provide such analysis for CHMP review.
- The MAH was requested to monitor cases with a medical history of angioedema/angioedema like reactions in the next PSURs of Rasilez/Rasilez HCT and a clearer definition of angioedema should be used.
- The MAH was requested to provide a cumulative analysis with the next Rasilez PSUR of all cases of angioedema/angioedema like reactions where aliskiren was co-administered with RAS blockers (ACE inhibitors as well as ARBs).
- Given the seriousness of the ADR ‘angioedema’, the PhVWP agreed that also SPC section 4.3 “Contraindications” should be updated in line with the SPC of the ACE inhibitors. Therefore, it was agreed that “Hereditary or idiopathic angioedema” should be added as a new contraindication to the Rasilez, Riprazo, Sprimeo and Rasilez HCT SPCs.

- Finally, given that co-administration of aliskiren and ACE inhibitors/ARBs is quite frequent in clinical practice and considering the cases of angioedema reported in this review regarding patients on aliskiren co-administered with RAS blockers, the working party members considered that the MAH should be asked to discuss potential interactions between aliskiren and ACE inhibitors and/or ARBs with the view of updating the Rasilez, Riprazo, Sprimeo and Rasilez HCT SPCs.

The requested information has now been provided as follow–up measures by the MAH and is currently undergoing assessment by the CHMP.

Changes to Product Information

Following the outcome of the PhVWP/CHMP review, the MAH was requested to submit a variation to update the SPC as outlined below:

4.3 Contraindications

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History of angioedema with aliskiren.

Hereditary or idiopathic angioedema

4.4 Special warnings and precautions for use

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Angioedema

As with other agents acting on the renin-angiotensin system (RAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat, and/or tongue) ~~has~~ have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicines that can cause angioedema, including RAS blockers (ACE inhibitors or ARBs) (see section 4.8).

Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (See sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If angioedema occurs, Rasilez should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to ~~ensure~~ maintain patent airways should be provided.

4.8 Undesirable effects

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Table 1

Gastrointestinal disorders	
Common:	Diarrhoea
Skin and subcutaneous tissue disorders	
Uncommon:	Rash
Rare:	Angioedema

Angioedema has occurred during treatment with Rasilez. In controlled clinical trials, angioedema occurred rarely during treatment with Rasilez with rates comparable to treatment with placebo or hydrochlorothiazide.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat, and/or tongue) have also been reported in post-marketing experience ~~(frequency unknown)~~. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicines known to cause angioedema, including RAS blockers (ACE inhibitors or ARBs).

In the event of any signs suggesting a hypersensitivity reaction/angioedema ~~an allergic reaction~~ (in particular difficulties in breathing, or swallowing, or swelling of the face, extremities, eyes, lips and/or tongue) patients should discontinue treatment and contact the physician (see section 4.4).

Benefit-risk assessment

The MAH has applied for a worksharing type IB variation to update the Rasilez, Riprazo, Sprimeo and Rasilez HCT SPCs in line with the PhVWP/CHMP request, as discussed above. The variation application is approvable. The benefit risk balance remains unchanged.

2. Conclusion

On 16 December 2010 the CHMP considered this Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics.

Variations requested		**Type**
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